

10/668,326

=> d his

(FILE 'HOME' ENTERED AT 09:36:50 ON 09 APR 2004)

FILE 'REGISTRY' ENTERED AT 09:37:00 ON 09 APR 2004

E HYDROMORPHONE/CN

L1 1 S E3

L2 STRUCTURE UPLOADED

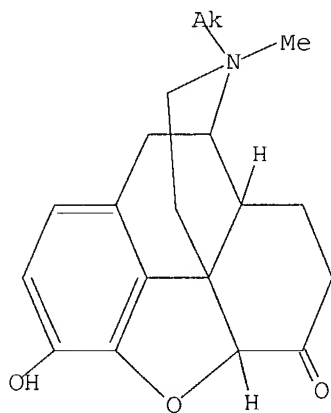
L3 0 S L2

L4 0 S L2 FULL

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L2 HAS NO ANSWERS

L2 STR



Structure attributes must be viewed using STN Express query preparation.

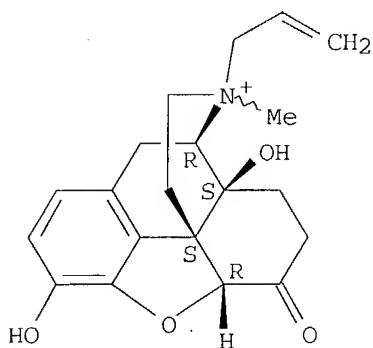
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STN - STRUCTURE SEARCH
4.9.04

10/668,326

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5 α)- (9CI) (CA INDEX NAME)

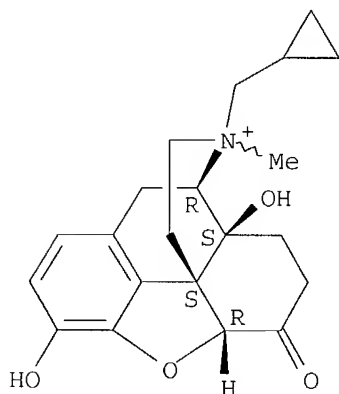
Absolute stereochemistry.



RN 73232-52-7 CAPLUS

CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 163 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1982:28431 CAPLUS

DOCUMENT NUMBER: 96:28431

TITLE: Comparison of the effects of the hydrochloride and methiodide of naloxone on endotoxin shock in the anesthetized rat

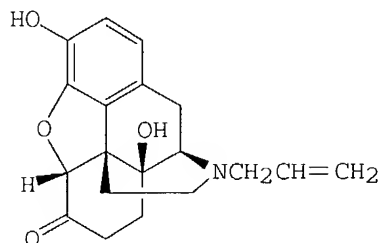
AUTHOR(S): Rios, L.; Jacob, J.

CORPORATE SOURCE: Unite Pharmacol. Toxicol., Inst. Pasteur, Paris, 75724, Fr.

SOURCE: Archives de l'Institut Pasteur de Tunis (1981), 58(3-4), 313-27

DOCUMENT TYPE:
LANGUAGE:
GI

Journal
French



I

AB In the anesthetized rat, *Escherichia coli* endotoxin-induced shock was characterized by long-lasting hypotension. Administration of (-)-naloxone-HCl (I-HCl) [357-08-4] (10 mg/kg, i.v.) reversed the hypotension for approx. 1 h, whereas I methiodide [73232-48-1] did not have this effect. I-HCl also produced some tachycardia and some awakening of animals that was not observed with I methiodide. Since the hydrochloride salt of I crosses the blood-brain barrier easier than the quaternary ammonium salt (I methiodide), it appears that I-HCl acts at a central site possibly through antagonism of β -endorphin release by endotoxin.

IT 73232-48-1

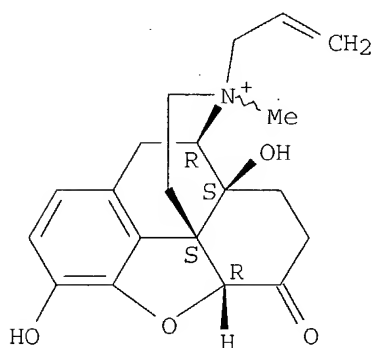
RL: BIOL (Biological study)

(endotoxin shock response to, naloxone hydrochloride in relation to)

RN 73232-48-1 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, iodide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● I -

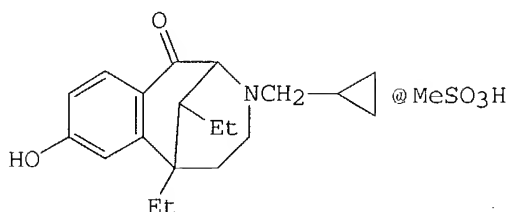
L4 ANSWER 164 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1981:525970 CAPLUS

DOCUMENT NUMBER: 95:125970

TITLE: Pharmacological analysis of the discriminative stimulus characteristics of ethylketazocine in the

AUTHOR(S): rhesus monkey
 Hein, David W.; Young, Alice M.; Herling, Seymore;
 Woods, James H.
 CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, 48109,
 USA
 SOURCE: Journal of Pharmacology and Experimental Therapeutics
 (1981), 218(1), 7-15
 CODEN: JPETAB; ISSN: 0022-3565
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 GI



AB Rhesus monkeys were trained to discriminate between the i.m. injection of 10 µg/kg of ethylketazocine methane sulfonate (EKC) (I) [71630-25-6] and saline. Twenty consecutive responses upon the right or left lever were reinforced with food, contingent upon whether EKC or saline was administered before the session. The discriminative stimulus effect of EKC was stereospecific since the d-isomer of EKC [78853-53-9] did not produce EKC-appropriate responding over a wide range of doses, including doses 1000-fold greater than required for racemic EKC. In addition, UM 1072 [57286-96-1] produced the EKC-discriminative effect, whereas its all-S enantiomer, UM 1071-S [57236-93-8], at 1000-fold higher doses did not. In 2 monkeys, the EKC-discriminative stimulus was reversed by naltrexone-HCl [16676-29-2] whereas in 2 others it was not. The EKC-discriminative stimulus appears to be centrally mediated since nalorphine-HCl [57-29-4] produced the stimulus but N-methylnalorphinium bromide [58046-46-1] did not. Furthermore, naltrexone methobromide [73232-52-7] failed to reverse the discriminative effects of EKC. Other drugs that produced discriminative effects similar to those of EKC were the narcotic agonists, ketazocine methane sulfonate [71697-06-8] and UM 909 [72174-02-8] and the mixed agonist-antagonists, cyclazocine [3572-80-3], cyclorphan-HCl [4163-28-4], SKF-10,047-HCl [74957-58-7] and nalorphine. Ketamine-HCl [1867-66-9] and phenycyclidine-HCl [956-90-1] produced EKC-appropriate responses in 2 of 4 monkeys. In contrast, morphine sulfate [64-31-3], codeine phosphate [52-28-8], pentazocine [359-83-1], etorphine-HCl [13764-49-3], levorphanol tartrate [125-72-4], and meperidine-HCl [50-13-5] as well as the nonnarcotics Na pentobarbital [57-33-0], dextrorphan tartrate [125-72-4], and apomorphine-HCl [314-19-2] produced primarily saline-appropriate responding over a wide range of doses, including those that markedly reduced the rate of responding. Thus, the EKC-discriminative stimulus in the rhesus monkey identifies a pharmacol. class of narcotics that differ from morphine.

IT 73232-52-7

RL: BIOL (Biological study)

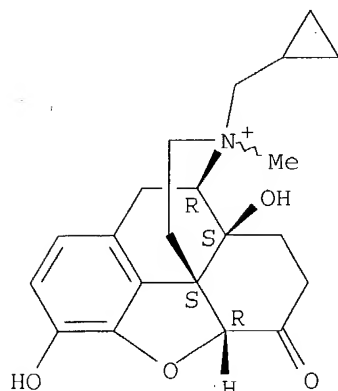
(behavior response to, discriminative stimulus characteristics in, ethylketazocine in relation to)

RN 73232-52-7 CAPLUS

CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α)- (9CI) (CA INDEX NAME)

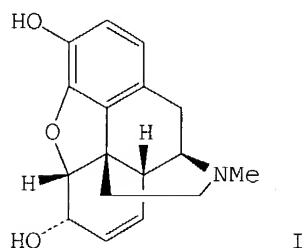
10/668,326

Absolute stereochemistry.



● Br⁻

L4 ANSWER 165 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1981:490941 CAPLUS
DOCUMENT NUMBER: 95:90941
TITLE: Opiates act centrally on GH and PRL release
AUTHOR(S): Panerai, Alberto E.; Casanueva, Felipe; Martini, Alberto; Mantegazza, Paolo; Di Giulio, Anna Maria
CORPORATE SOURCE: Dep. Pharmacol., Univ. Milano, Milan, Italy
SOURCE: Endocrinology (1981), 108(6), 2400-2
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Male rats were treated with morphine-HCl (I-HCl) [52-26-6] after pretreatment with saline with either the opiate antagonist naloxone-HCl [357-08-4] or the quaternary derivative naloxone Me bromide (Naloxone-Br) [73232-49-2], the latter of which does not cross the blood brain barrier. I elicited a clear cut increase in prolactin [9002-62-4] and growth hormone [9002-72-6] release after pretreatment with Naloxone-Br, but not after pretreatment with naloxone-HCl. Naloxone-Br, however, was able to inhibit the effect of morphine when administered directly in the brain ventricles. Morphine Me iodide [14054-17-2], which does not cross the blood brain barrier was administered. The quaternary I derivative was ineffective in eliciting growth hormone and prolactin release when administered peripherally, but was effective when administered intraventricularly.

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IT 73232-49-2

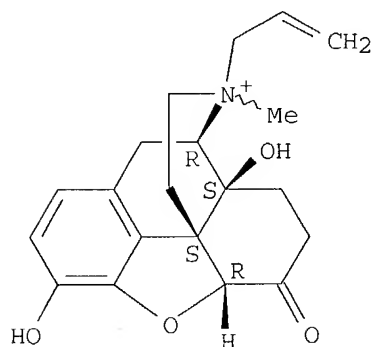
RL: BIOL (Biological study)

(of brain, growth hormone and prolactin release response to)

RN 73232-49-2 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

L4 ANSWER 166 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1981:418194 CAPLUS

DOCUMENT NUMBER: 95:18194

TITLE: Quaternary naltrexone: evidence for the central mediation of discriminative stimulus effects of narcotic agonists and antagonists

AUTHOR(S): Valentino, Rita J.; Herling, Seymore; Woods, James H.; Medzihradsky, Fedor; Merz, Herbert

CORPORATE SOURCE: Dep. Pharmacol., Univ. Michigan, Ann Arbor, MI, USA

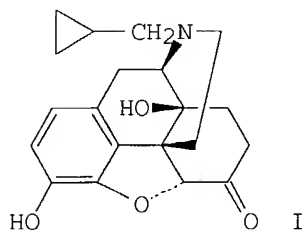
SOURCE: Journal of Pharmacology and Experimental Therapeutics (1981), 217(3), 652-9

CODEN: JPETAB; ISSN: 0022-3565

DOCUMENT TYPE: Journal

LANGUAGE: English

GI



AB A quaternary derivative to naltrexone (I) [73232-52-7] was compared to naltrexone [16590-41-3] in its ability to antagonize the discriminative stimulus effects of narcotics in pigeons and rhesus monkeys and to substitute as a discriminative stimulus for naltrexone in narcotic-naive pigeons and in pigeons chronically administered morphine

sulfate [64-31-3]. I was ineffective as an antagonist of the morphine discriminative stimulus in pigeons and of the etorphine discriminative stimulus in rhesus monkeys when administered in doses 300 times greater than the effective antagonist dose of naltrexone. When tested in narcotic-naive pigeons trained to discriminate naltrexone (32 mg/kg) from saline, the quaternary analog of naltrexone failed to produce discriminative control of behavior comparable to that produced by naltrexone, although I was as effective and as potent as naltrexone in suppressing the rate of responding. In addition, doses of I up to 32 mg/kg did not generalize to naltrexone in pigeons that were chronically treated with morphine (100 mg/kg/day) and trained to discriminate 0.10 to 0.32 mg/kg of naltrexone from saline. Although I was ineffective in these drug discrimination assays, it did displace the stereospecific binding of [3H]etorphine from rat brain membranes. In addition, I was as effective as naltrexone in antagonizing the effect of morphine upon the elec. induced contraction of the isolated guinea pig ileum and in eliciting a contraction of ilea isolated from morphine-treated guinea pigs. Only a potency difference distinguished naltrexone from its quaternary derivative in these in vitro assays, with I being 26 to 77 times less potent. Because the efficacy and potency of I in the behavioral assays were much less than would be predicted on the basis of the activity of the compound in vitro, the discriminative stimulus effects of narcotics and the antagonism of these effects by naltrexone, and the discriminative stimulus effects of narcotic antagonists in organisms chronically treated with morphine, are probably the result of central mechanisms.

IT 73232-52-7

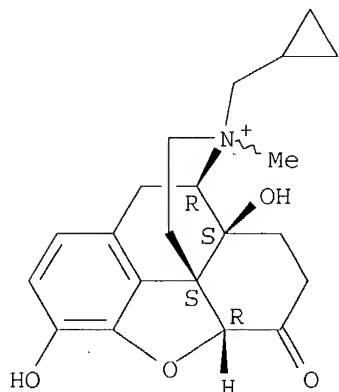
RL: BIOL (Biological study)

(discriminative stimulus activity of, central mechanisms in relation to)

RN 73232-52-7 CAPLUS

CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

L4 ANSWER 167 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN

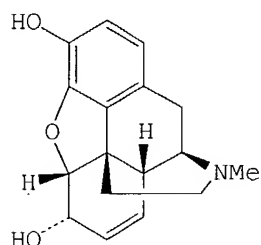
ACCESSION NUMBER: 1981:202623 CAPLUS

DOCUMENT NUMBER: 94:202623

TITLE: Inhibition of gastrointestinal transit and antinociceptive effects of morphine and FK 33-824 in rats are differently prevented by naloxone and by its

10/668,326

AUTHOR(S): N-methyl quaternary analog
Ferretti, P.; Bianchi, G.; Tavani, A.; Manara, L.
CORPORATE SOURCE: Lab. Drug Metab., Ist. Ric. Farmacol. "Mario Negri",
Milan, 20157, Italy
SOURCE: Research Communications in Substances of Abuse (1981),
2(1), 1-11
CODEN: RCSADO; ISSN: 0193-0818
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



AB Thirty minutes after s.c. administration to rats of 0.15-10 mg/kg morphine-HCl (I-HCl) [52-26-6] or 0.005-5 of the enkephalin-like peptide FK 33-824 [64854-64-4], gastrointestinal transit of a forced charcoal meal was dose-dependently inhibited. However, considerably less (.apprx.100 times) FK 33-824 than I was sufficient to elicit threshold and even substantial (over 50%) inhibition. The marked transit inhibition (to < 40% of control) caused by a small i.p. dose (0.04 mg/kg) of either drug, was prevented almost completely in rats pretreated with the N-methyl quaternary analog of naloxone [73232-49-2] (1 mg/kg, i.p.). Gastrointestinal transit and nociceptive reaction to the hot-plate (55°), were blocked in rats given FK 33-824 (2.5 mg/kg, i.v.) or double this dose of I; pretreatment with 1 mg/kg naloxone-HCl [357-08-4] (i.p.) fully prevented both effects of I and antinociception by FK 33-824 whose intestinal action however was only partially antagonized. I-induced inhibition of gastrointestinal transit was substantially reversed but there was no impairment of the drug's antinociceptive action when naloxone was replaced with its N-Me quaternary analog (4 mg/kg) which under the same conditions did not affect FK 33-824's efficacy on these 2 endpoints. Apparently, FK 33-824 has potent opiate-like action on gastrointestinal transit in rats and that, unlike naloxone, its N-Me quaternary analog can selectively prevent the effect of I on the gut without affecting antinociception.

IT 73232-49-2

RL: BIOL (Biological study)

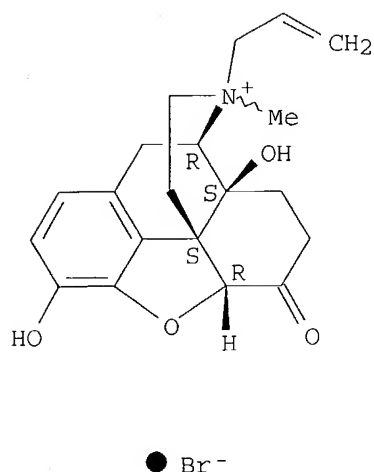
(antinociception and gastrointestinal transit from FK 33-824 and morphine inhibition by)

RN 73232-49-2 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5 α)-(9CI) (CA INDEX NAME)

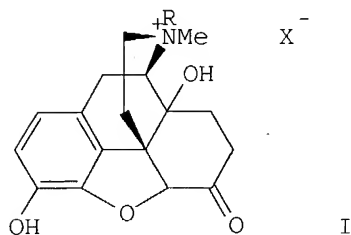
Absolute stereochemistry.

10/668,326



L4 ANSWER 168 OF 168 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 1980:147018 CAPLUS
 DOCUMENT NUMBER: 92:147018
 TITLE: Quaternary derivatives of noroxymorphone which relieve intestinal immobility
 INVENTOR(S): Goldberg, Leon I.; Merz, Herbert; Stockhaus, Klaus
 PATENT ASSIGNEE(S): Boehringer Ingelheim G.m.b.H., Fed. Rep. Ger.
 SOURCE: U.S., 6 pp.
 CODEN: USXXAM
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4176186	A	19791127	US 1978-928821	19780728
PRIORITY APPLN. INFO.: GI			US 1978-928821	19780728



AB The noroxymorphone derivs. I (R = allyl, chloroalkyl, cyclopropylmethyl, HC.tplbond.CCH2; X = Cl, Br, iodo, MeSO₄) were prepared. Thus, N-allylnoroxymorphone-HCl was treated with NH₃ followed by MeI to give I (R = alkyl, X = iodide). I prevent intestinal mobility inhibiting side-effects of narcotic analgesics (no data).
 IT 73232-48-1P 73232-49-2P 73232-51-6P
 73232-52-7P 73232-53-8P 73232-54-9P
 73232-56-1P 73246-51-2P
 RL: SPN (Synthetic preparation); PREP (Preparation)

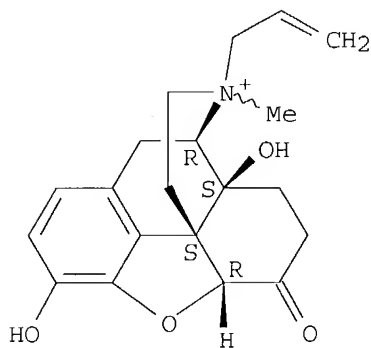
10/668,326

(preparation of)

RN 73232-48-1 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, iodide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

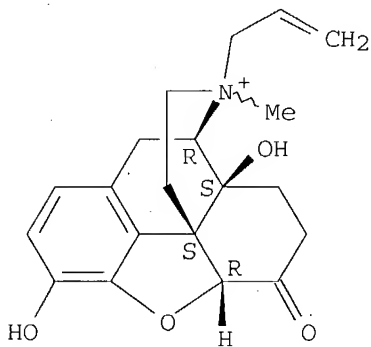


● I⁻

RN 73232-49-2 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, bromide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

RN 73232-51-6 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propenyl)-, (5 α)-, methyl sulfate (salt) (9CI) (CA INDEX NAME)

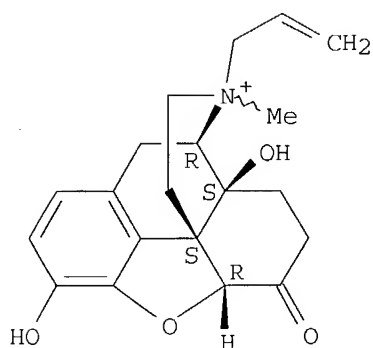
CM 1

CRN 73232-50-5

CMF C20 H24 N O4

Absolute stereochemistry.

10/668,326



CM 2

CRN 21228-90-0

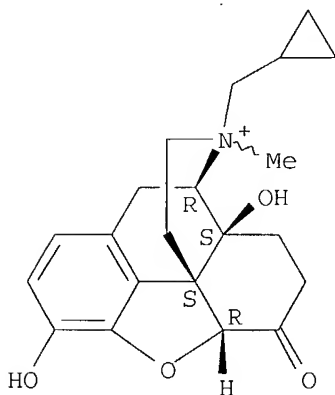
CMF C H3 O4 S

Me-O-SO₃⁻

RN 73232-52-7 CAPLUS

CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



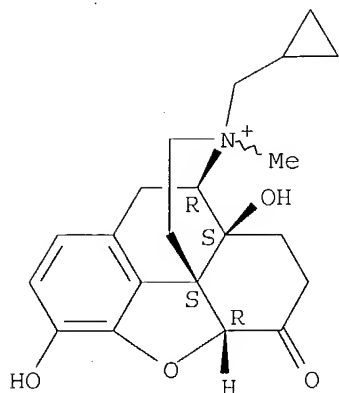
● Br⁻

RN 73232-53-8 CAPLUS

CN Morphinanium, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, iodide, (5α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

10/668,326

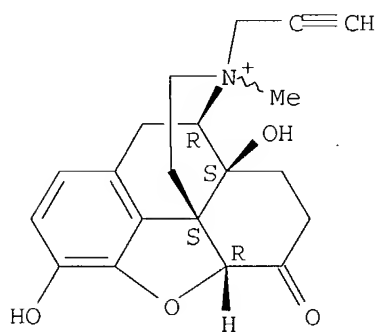


● I⁻

RN 73232-54-9 CAPLUS

CN Morphinanium, 4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-17-(2-propynyl)-, bromide, (5 α)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● Br⁻

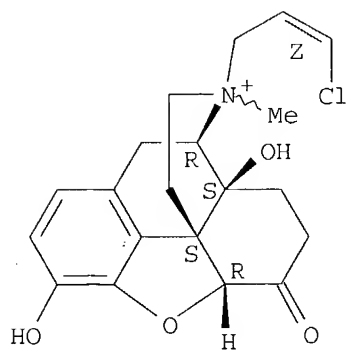
RN 73232-56-1 CAPLUS

CN Morphinanium, 17-(3-chloro-2-propenyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, [5 α ,17(Z)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry as shown.

10/668,326

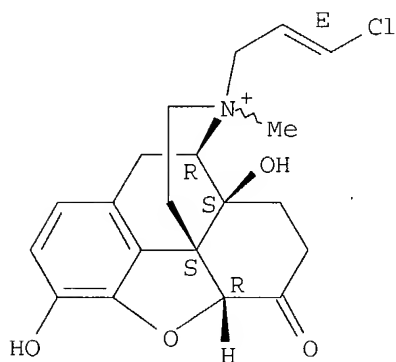


● Br⁻

RN 73246-51-2 CAPLUS

CN Morphinanium, 17-(3-chloro-2-propenyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, bromide, [5 α ,17(E)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



● Br⁻

=> d his

(FILE 'HOME' ENTERED AT 10:01:03 ON 09 APR 2004)

FILE 'REGISTRY' ENTERED AT 10:01:14 ON 09 APR 2004

L1 STRUCTURE UPLOADED

L2 1 S L1

L3 35 S L1 FULL

FILE 'CAPLUS' ENTERED AT 10:01:57 ON 09 APR 2004

L4 168 S L3

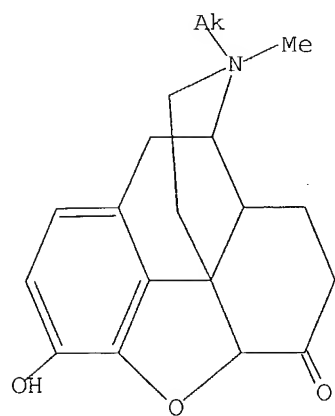
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L1 HAS NO ANSWERS

10/668,326

L1

STR



Structure attributes must be viewed using STN Express query preparation.

=>

Day : Friday
Date: 4/9/2004
Time: 09:10:59

PALM INTRANET

Inventor Name Search Result

Your Search was:

Last Name = KYLE

First Name = DONALD

Application#	Patent#	Status	Date Filed	Title	Inventor Name 51
60499314	Not Issued	018	08/28/2003	METHODS OF ANTIBODY ENGINEERING USING ANTIBODY DISPLAY REGIONS	KYLE, DONALD J.
60484881	Not Issued	020	07/03/2003	THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN	KYLE, DONALD J.
60416582	Not Issued	020	10/08/2002	THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN	KYLE, DONALD
60413254	Not Issued	020	09/25/2002	N-SUBSTITUTED HYDROMORPHONES AND THE USE THEREOF	KYLE, DONALD J.
60413148	Not Issued	020	09/25/2002	THERAPEUTIC AGENTS USEFUL FOR TREATING PAIN	KYLE, DONALD
60411084	Not Issued	020	09/17/2002	THIADIAZOLEPIPERAZINE COMPOUNDS USEFUL FOR TREATING OR PREVENTING PAIN	KYLE, DONALD J.
60411043	Not Issued	020	09/17/2002	PIPERAZINE COMPOUNDS USEFUL FOR TREATING OR PREVENTING PAIN	KYLE, DONALD J.
60411030	Not Issued	020	09/17/2002	CYANOIMINOPIPERAZINE COMPOUNDS, COMPOSITIONS THEREOF AND USES THEREFOR	KYLE, DONALD
60399702	Not Issued	159	08/01/2002	ARYL SUBSTITUTED BICYCLO-BENZOHETEROCYCLIC COMPOUNDS AND THEIR USE AS SODIUM CHANNEL BLOCKERS	KYLE, DONALD J.
60399697	Not Issued	159	08/01/2002	AMINE SUBSTITUTED ARYL COMPOUNDS AND THEIR USE AS SODIUM CHANNEL BLOCKERS	KYLE, DONALD J.
60399458	Not Issued	159	07/31/2002	ARYL SUBSTITUTED BENZIMIDAZOLES AND THEIR USE AS SODIUM CHANNEL BLOCKERS	KYLE, DONALD J.
60399435	Not	159	07/31/2002	ARYL SUBSTITUTED HYDANTOIN	KYLE,

	Issued			COMPOUNDS AND THEIR USE AS SODIUM CHANNEL BLOCKERS	DONALD J.
<u>60360172</u>	Not Issued	159	03/01/2002	THIADIAZOLEPIPERAZINE COMPOUNDS USEFUL FOR TREATING OR PREVENTING PAIN	KYLE, DONALD J.
<u>60352855</u>	Not Issued	159	02/01/2002	PIPERAZINE COMPOUNDS USEFUL FOR TREATING OR PREVENTING PAIN	KYLE, DONALD J.
<u>60305099</u>	Not Issued	159	07/16/2001	ARYL SUBSTITUTED THIAZOLIDINONES AND THE USE THEREOF	KYLE, DONALD J.
<u>60284676</u>	Not Issued	159	04/18/2001	SUBSTITUTED QUINOLINE COMPOUNDS	KYLE, DONALD
<u>60284675</u>	Not Issued	159	04/18/2001	SPIROPYRAZOLE COMPOUNDS	KYLE, DONALD
<u>60284674</u>	Not Issued	159	04/18/2001	CYCLIC SULFONE COMPOUNDS	KYLE, DONALD
<u>60284670</u>	Not Issued	159	04/18/2001	SPIROINDENE AND SPIROINDANE COMPOUNDS	KYLE, DONALD
<u>60284669</u>	Not Issued	159	04/18/2001	BENZOXAZOLONE COMPOUNDS	KYLE, DONALD
<u>60284668</u>	Not Issued	159	04/18/2001	SUBSTITUTED INDOLE COMPOUNDS	KYLE, DONALD
<u>60284667</u>	Not Issued	159	04/18/2001	BENZIMIDAZOLONE COMPOUNDS	KYLE, DONALD
<u>60284666</u>	Not Issued	159	04/18/2001	SUBSTITUTED BENZIMIDAZOLE COMPOUNDS	KYLE, DONALD
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